What's new for the clinician – summaries of recently published papers

1. Ivermectin for the Treatment of COVID-19: A Systematic Review and Meta-analysis of Randomized Controlled Trial

Roman YM, Burela PA, Pasupuleti V, Piscoya A, Vidal JE, Hernandez AV. Ivermectin for the Treatment of Coronavirus Disease 2019: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Clinical Infectious Diseases. 2021 Jun 28. ciab591. doi: 10.1093/cid/ciab591.

INTRODUCTION

To date, very few treatments have been demonstrated to reduce the burden of morbidity and mortality from COVID-19. Although corticosteroids have been proven to reduce mortality in severe disease,[1] there has been little convincing evidence on interventions that may prevent disease, reduce hospitalizations, and reduce the numbers of people progressing to critical disease and death.

Ivermectin is a well-known medicine that is approved as an antiparasitic by the World Health Organization and the US Food and Drug Administration. It is widely used in low- and middle-income countries to treat worm infections. Also used for the treatment of scabies and lice, it is one of the World Health Organization's Essential Medicines.[1] With total doses of ivermectin distributed apparently equalling one-third of the present world population,[1] ivermectin at the usual doses (0.2–0.4 mg/kg) is considered extremely safe for use in humans.[1] In addition to its antiparasitic activity, it has been noted to have antiviral and anti-inflammatory properties, leading to an increasing list of therapeutic indications.

South African authorities approved the use of a drug used to control parasites in humans and livestock to treat coronavirus patients. Additionally, in January 2021, the South African Health Products Regulatory Authority

Veerasamy Yengopal: *BChD, BScHons, MChD*, *PhD*, Community Dentistry Department, School of Oral Health Sciences, University of Witwatersrand, Medical School, no. 7 York Road, Parktown 2193, South Africa.
ORCID Number: 0000-0003-4284-3367
Email: veerasamy.yengopal@wits.ac.za

(SAHPRA) announced that ivermectin, would be allowed for use on compassionate grounds in a controlled-access program. Ivermectin locally has been used for the prevention and/or management of Covid-19 infection. This has resulted in a huge black market trade of ivermectin in South Africa as many health professionals and others have taken to social media and other platforms to profile this drug as an effective treatment for the covid-19 viral infection. Roman and colleagues (2021)[1] conducted a systematic review and meta-analysis to evaluate treatment effects of Ivermectin (IVM) on clinical outcomes and adverse events (AEs) in people with COVID-19.

MATERIALS AND METHODS

A search strategy was developed for use in 5 databases: PubMed-MEDLINE, EMBASE-OVID, Scopus, Web of Science, the Cochrane Library; and preprints from www.medrxiv.org, www.preprints.org, and www.ssrn.com. The search was limited until 22 March 2021. Randomized clinical trials (RCTs) in any language reporting benefit or harm outcomes of IVM as treatment in patients with COVID-19, both non-hospitalized and hospitalized, irrespective of COVID-19 severity were considered for inclusion. Studies assessing prophylaxis for COVID-19 infection were excluded. Controls were the standard of care (SOC) or placebo. Two investigators independently screened titles and abstracts and then assessed full texts of selected abstracts. Discrepancies were resolved through discussion or by a third investigator.

Primary outcomes were all-cause mortality rate, length of hospital stay (LOS), and adverse events (AEs). Secondary outcomes were SARS-CoV-2 clearance

on respiratory samples, clinical improvement, need for mechanical ventilation, and severe AEs (SAEs).

Two investigators independently extracted the following data: country, sample size, dose and duration of IVM treatment, type of control group (SOC vs placebo), COVID-19 severity, percentage of reverse-transcription polymerase chain reaction (RT-PCR) results positive for SARS-CoV-2, study setting (hospitalized vs non-hospitalized), mean age, proportions of female patients and patients with hypertension, diabetes mellitus, or cardiovascular disease, outcomes, and duration of follow-up. COVID-19 disease severity was defined as mild, moderate, or severe according to the WHO classification. Discrepancies were resolved through discussion and consensus.

Two investigators independently assessed the risk of bias (RoB) using the Cochrane Risk of Bias 2.0 tool for RCTs; disagreements were resolved by discussion with a third investigator. This tool evaluates 5 domains of bias: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results. The RoB for each of the 5 domains and overall was described as low, some concerns, or high.

Inverse variance random effect meta-analyses were performed to evaluate the effects of IVM versus control on outcomes. Effects of meta-analyses were reported as relative risk (RR) for dichotomous outcomes and as mean difference for continuous outcomes.

The heterogeneity of effects among studies was quantified using the I2 statistic (I2 >60% indicates high heterogeneity). Sensitivity analyses excluding RCTs with shorter follow-up (i.e., <21 days) were planned for the primary outcomes. The certainty or quality of evidence (QoE) was evaluated using GRADE methods, which cover RoB, inconsistency, indirectness, imprecision, and publication bias

RESULTS

The search yielded 256 citations with an additional 9 citations identified in preprint Web pages; 253 records were excluded. After assessing 12 full texts, the researchers identified 10 RCTs (n = 1173). Two full texts were excluded; there was no control group in one of these studies, and an outcome of no interest (duration of fever) was the only outcome reported in the other.

One RCT was conducted in Spain and the other 9 were conducted in low- and middle-income countries. Sample sizes for RCTs ranged from 24 to 398 patients. IVM doses were heterogeneous in terms of total doses (ranging from 12 mg to 210 mg) and duration (ranging from 1 to 5 days). Controls were the SOC in 5 RCTs and placebo in 5. Most RCTs were conducted in patients with mild COVID-19: mild in all or most patients in 8 RCTs moderate in 1], and mild and moderate in[1].

All patients had RT-PCR results positive for SARS-CoV-2 at baseline, except in 2 RCTs. Mean or median ages

ranged from 26 to 56 years, and the percentage of female patients from 15% to 78% and most patients did not have hypertension, diabetes mellitus, or cardiovascular disease. Evaluated outcomes were also heterogeneous across RCTs, and the duration of follow-up ranged from 5 days to 30 days

Eight RCTs had a high risk of bias (RoB), one had some concerns of bias in the randomization process, and one had a low RoB.

IVM, compared with control treatment, did not have an effect on:
- the all-cause mortality rate in 5 RCTs (RR, 0.37 [95% CI, 0.12–1.13]; I2 = 16%; very low quality of evidence)
- length of hospital stay (LOS), in 3 RCTs (mean difference, 0.72 days [–0.86 to 2.29 days]; I2 = 0%; very low quality of evidence)
- Adverse events (AEs) in 3 RCTs (RR, 0.95 [0.85–1.07]; I2 = 0%; low quality of evidence)
- Compared with control treatment, IVM had no effect on severe adverse events (SAEs) in 3 RCTs (RR, 1.39 [95% CI, 0.36–5.30]; I2 = 0%; low quality of evidence or on viral clearance in 4 RCTs (RR, 0.96, [.79–1.16]; I2 = 0%; low quality of evidence

Subgroup analyses by severity of COVID-19 disease or risk of bias (RoB) were consistent with main analyses. Sensitivity analyses excluding studies with follow-up <21 days showed similar effects as primary analyses for all-cause mortality rate and length of hospital stay (LOS). The statistical heterogeneity of effects for all-cause mortality was 0% in sensitivity analysis.

CONCLUSIONS

The systematic review with meta-analyses found that, compared with standard of care (SOC) or placebo, IVM did not reduce all-cause mortality rate, length of hospital stay (LOS), respiratory viral clearance, adverse events (AEs), or severe adverse events (SAEs) in RCTs of patients with mild to moderate COVID-19. The reviewers did not find data about IVM effects on clinical improvement or the need for mechanical ventilation. In view of the current evidence, the reviewers concluded that IVM is not a viable option for treating patients with COVID-19, and should be used only within clinical trials.

Implications of practice

Many patients will ask oral health professionals for their views on the efficacy of IVM for the treatment of COVID-19. Responses and/or opinions should be based on high quality evidence as used in systematic reviews with meta-analyses of randomised clinical trials.

Reference
1. Roman YM, Burela PA, Pasupuleti V, Piscoya A, Vidal JE, Hernandez AV. Ivermectin for the Treatment of Coronavirus Disease 2019: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Clinical Infectious Diseases. 2021 Jun 28. ciab591. doi: 10.1093/cid/ciab591.